

FILE 'REGISTRY' ENTERED AT 11:43:58 ON 01 JUN 2007

L1 1 S 94724-12-6/RN  
L2 ( 158065)ANTIGEN  
L3 0 S L1 AND ANTIGEN  
L4 ( 9)IMMUNOGEN  
L5 0 S L1 AND IMMUNOGEN  
L6 ( 578)VACCINE  
L7 0 S L1 AND VACCINE

FILE 'REGISTRY' ENTERED AT 11:48:00 ON 01 JUN 2007

SET TERMSET E#  
DEL SEL Y  
SEL L1 1 RN  
L8 1 S E1/RN  
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FILE 'CAPLUS' ENTERED AT 11:48:05 ON 01 JUN 2007

L9 4 S L8

*Ynone*



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## Th1 and Th2 Balance, Regulation, and Involvement in Disease

Cytokines are the hormonal messengers responsible for most of the biological effects in the immune system, such as cell-mediated immunity and allergic type responses. T lymphocytes are a major source of cytokines. These cells bear antigen-specific receptors on their cell surface to allow recognition of foreign pathogens. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as helper T cells, and these are regarded as being the most prolific cytokine producers. This subset can be further subdivided into Th1 and Th2, and the cytokines they produce are known as Th1-type cytokines and Th2-type cytokines.

### Th1 cells

Type 1 helper T cells are characterized by the production of pro-inflammatory cytokines like IFN- $\gamma$ , IL-2, and TNF- $\beta$ . Th1 cells are involved in cell-mediated immunity. The cytokines produced by Th1 cells stimulate the phagocytosis and destruction of microbial pathogens.

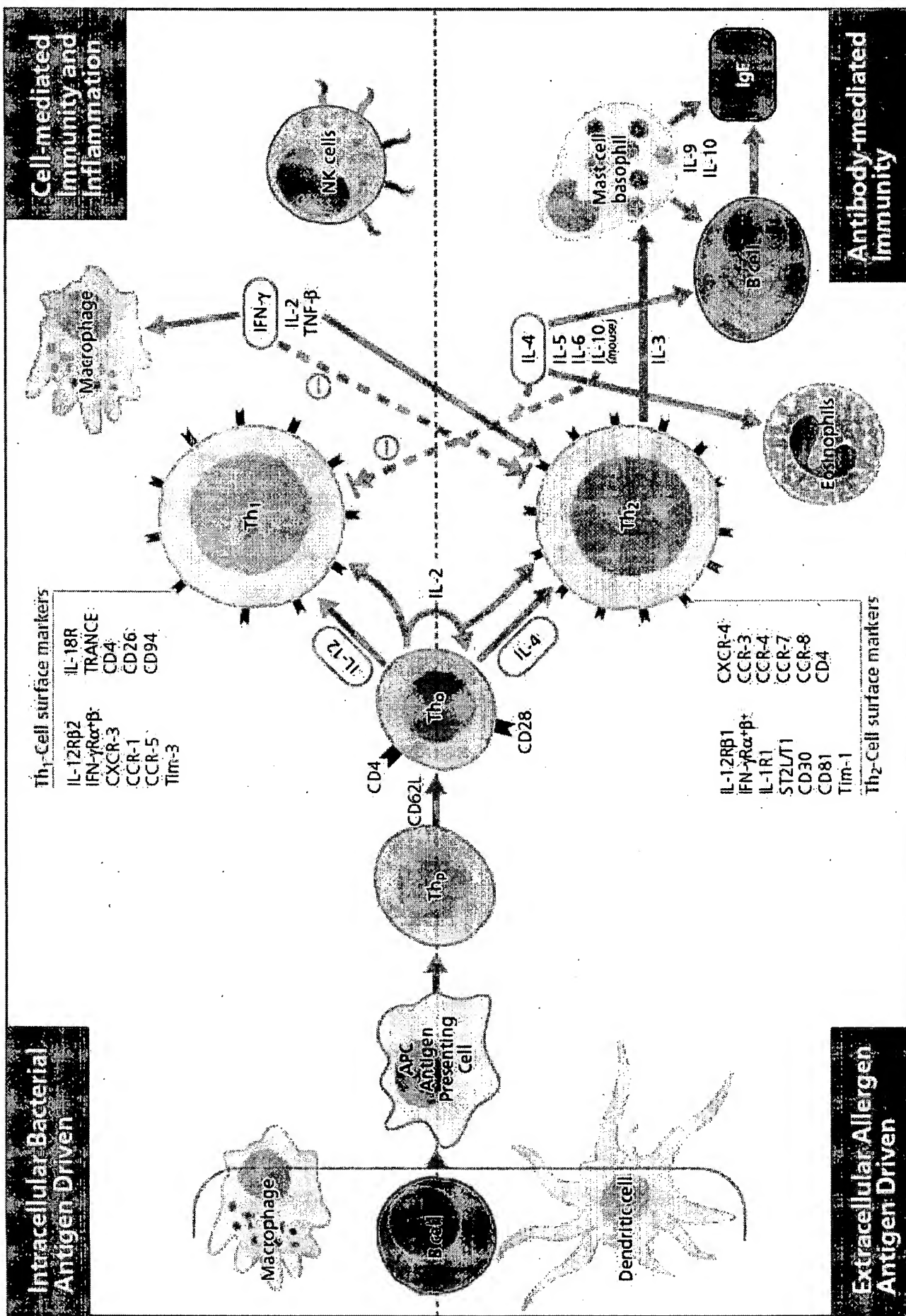
Several chronic inflammatory diseases have been described as Th1 dominant diseases i.e. multiple sclerosis, diabetes, and rheumatoid arthritis.

### Th2 cells

Type 2 helper T cells are characterized by the production of IL-4, IL-5, IL-9, IL-10, and IL-13. Th2 cells are thought to play a role in allergy responses. Cytokines like IL-4 generally stimulate the production of antibodies directed toward large extracellular parasites. IL-5 stimulates eosinophil responses, also part of the immune response toward large extracellular parasites. Atrophy and allergy are thought to be Th2 dominant conditions.

Improved understanding of Th1 and Th2 differentiation will improve our overall understanding of the immune system, its response to

infection and aberrant responses that lead to disease.



When Th1 cells produce IFN- $\gamma$ , this prompts the macrophages to produce TNF and toxic forms of oxygen which destroy the microorganisms within the phagosomes and lysosomes. On the other hand, when Th2 cells produce IL-4 and IL-10, these cytokines block the microbe killing that is activated by IFN- $\gamma$ .

The Th1/Th2 relationship has also been investigated in regards to transplantation. Th1 responses have been implicated in most forms of acute rejection and graft versus host disease, while Th2 responses have been variably associated with either protection or chronic rejection. However, cloned Th1 or Th2 cells have a similar capacity to reject skin grafts in experimental models, and regulatory T lymphocytes (Tr1/Treg cells) are now being implicated in protection and tolerance induction. The fetus is also analogous to an allograft and Th2 or Treg responses are thought to be protective, while Th1 responses may lead to resorption or spontaneous abortion.

שם	מיקום	פונקציה	מספר
CD26 (DPP IV, THAM)		Co-stimulatory molecule in T cell activation; associated marker of auto-immune diseases, adenosine deaminase-deficiency and HIV pathogenesis.	110
CD94		Assembled with other C-type lectins (NKG2) forms inhibitory or activating receptors for HLA class I.	43
CD119 (IFN-γ Rα)		IFN-γ regulates IL-18R α expression by preventing the negative effects of IL-4 and by inducing/maintaining IL-12 receptor β-2 expression.	35
CD183 (CXCR3)		Th1 cell surface marker. Cytokine that acts as a major participant in Th1-induced inflammation.	40
CD195 (CCR5; CCR5R5)		Regulates lymphocyte chemotaxis activation and trans-endothelial migration during inflammation. Neutralizes HIV infection. Acts as a co-receptor for HIV-1. Expressed on immature dendritic cells.	45
CD212 (IL-12RB2)		Th1 cell surface marker. The expression of this gene is up-regulated by IFNγ in Th1 cells, and plays a role in Th1 cell differentiation. The up-regulation of this gene is found to be associated with a number of infectious diseases, such as Crohn's disease and leprosy, which is thought to contribute to the inflammatory response and host defense.	97
GM-CSF		Pleiotropic cytokine that stimulates proliferation, maturation and function of hematopoietic cells. Produced by both Th1 and Th2 cells.	22
Granzyme B		Serine protease involved in the perforation of target cells and initiation of proteolysis that leads to apoptosis.	28
IFN-α		Antiviral and anti-proliferative activity.	19-26
IL-2 (TCGF)		IL-2 is the most potent T cell growth factor produced by Th1 cells.	15-17
IL-12		Inducer of proliferation and differentiation of Th1 cells. Dominant cytokine in Th1 development. Secreted by APCs, neutrophils, and keratinocytes. IL-4 and IL-10 inhibit IL-12 production by dendritic cells and macrophages.	70
IL-15 (IL-T)		IL-15 is a recently discovered cytokine with the ability to stimulate the proliferation activity of Th1 and/or Th2 lymphocytes.	14-15
IL-18R		A co stimulatory factor for the induction of IL-12-mediated IFNγ production by Th1 cells, but also can induce IL-4 production and thus facilitate the differentiation of Th2 cells.	93, 160, 220
IL-23		IL-23 affects Th1 differentiation by directly stimulating proliferative responses of Th1 cells.	
IL-27		A member of the IL-12 family mainly produced by activated monocytes and dendritic cells. IL-27 induces expression of the IL-12 receptor that in turn allows the Th1 response to be maintained.	
IL-27R (TCCR, WSX-1)		The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection.	
Lymphotoxin (LT-α)		Plays a role in the recruitment and activation of neutrophils and in lymphoid organogenesis. Being chemically similar to TNF, LT-α is also a mediator of a acute inflammatory responses. LT-α is made by T lymphocytes.	60-70
Perforin		Cytolytic mediator produced by killer lymphocytes.	70
t-bet		Transcription factor for Th1. Regulates the differentiation and function of lymphocytes.	58
Tim-3 (Havcr2, Timd3, Q8WW60)		Th1-specific cell surface protein. Tim-3 regulates macrophage activation and severity of an autoimmune disease.	16
TNF-β		Secreted by Th1 and cytotoxic T lymphocytes (Tc cells). It targets tumor cells, macrophages and neutrophils. Exerts inflammatory and cytotoxic effects.	19
TRANCE		Expressed on the surface of activated CD4+ Th1 cells. The ligand for TRANCE is RANK. TRANCE increases expression of inflammatory cytokines, such as IL-1 and IL-6, and secretion of IL-12, which can promote differentiation of CD4+ T cells into Th1 cells.	42

## Th2 Related Markers

Gene	Gene Name	Ref. (p2)
CCR3	Chemokine receptor for Th2. Binds to eotaxin, eotaxin-3, MCP-3, MCP-4, RANTES and MIP-1 $\delta$ . Alternative co receptor with CD4 for HIV-1 infection.	41
CCR4	Chemokine receptor for Th2. High affinity for TARC/SCYA17 and MDC/SCYA22.	41
CCR7 (CD197, EB1, Cmkbr7)	Th2 cell surface marker. Receptor for the MIP-3 $\beta$ chemokine, probable mediator of EBV effects on B lymphocytes.	46-52
CCR8 (Cy6, Cmkbr8)	CCR8 may contribute to the proper positioning of activated T cells within the antigenic challenge sites and specialized areas of lymphoid tissues. Th2 cell surface marker that plays a role in the control of Th2 responses, and may represent a potential target for treatment of allergic diseases.	41
CD4 (L3T4, W3/25)	Co-receptor in antigen-induced T-cell activation; thymic differentiation; regulation of T-8 lymphocyte adhesion; primary receptor for HIV. Th2 cell surface marker.	55
CD30 (Ber-H2, Ki-1)	Member of TNFR family, involved in negative selection of T cells in thymus and TCR mediated cell death; expressed on R-5 cells in Hodgkin's lymphomas. Th2 cell surface marker.	120
CD81 (TAPA-1)	Th2 cell surface marker. CD81 directly enhances Th1 and Th2 cell activation, but preferentially induces proliferation of Th2 cells upon long-term stimulation.	26
CD184 (CXCR4)	Homing receptor of hematopoietic progenitor cells; co-stimulation of B cells; induces apoptosis; involved with the entry of HIV-1. Cell surface marker for Th2 cells.	
CD278 (ICOS, H4, ALLIM, CRP-1)	ICOS costimulation leads to the induction of Th2 cytokines without augmentation of IL-2 production, suggesting a role for ICOS in Th2 cell differentiation and expansion.	40-70
c-maf	Transcription factor involved in the induction of production of IL-4.	
CRTH2	Th2 cell surface marker. Putative G protein-coupled receptor GPR44 (chemoattractant receptor-homologous molecule expressed on Th2 cells).	43
GATA-3	Transcription factor associated with induction of Th2 cells.	49
GM-CSF	Pleiotropic cytokine that stimulates proliferation, maturation, and function of hematopoietic cells. Produced by both Th1 and Th2 cells.	22
IFN- $\gamma$ R	Th2 cell surface marker.	60-65
IgD	IgD production by normal B cells is regulated positively by Th2 cytokines and negatively by Th1 cytokines.	
IL-1R	Th2 cell surface marker.	
IL-4 (BCDE, BCDf-1, BSF-1)	Th2 cytokine that stimulates antibody production by B cells. IL-4 stimulates Th2 activity and suppresses Th1 activity.	20
IL-5 (EDE, BCGFI, TRF)	Th2 cytokine that stimulates antibody production by B cells. A potent factor that drives bone marrow progenitor cells into IL-4-producing eosinophils.	32-34
IL-6 (BCSF, BSF-2)	Th2 inducing cytokine.	21-28
IL-9	IL-9 is a pleiotropic cytokine that can induce Th2 cytokine expression. IL-9 is also a candidate gene for asthma and atrophy.	36
IL-10 (CSIF)	Th2 cytokine that inhibits IFN- $\gamma$ , IL-2, and TNF- $\beta$ . Inhibits IL-12 production by dendritic cells thus inhibiting pre-Th cells from entering the Th1 pathway.	17-21
IL-12R $\beta$ 1	Th2 cell surface marker.	

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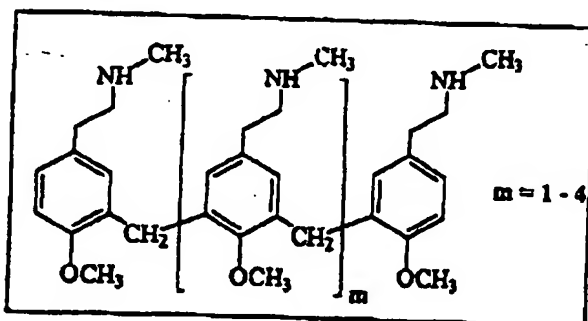
**COMPOUND 48/80**  
Sigma product number C2313

**CAS NUMBER:** 94724-12-6

**PHYSICAL DESCRIPTION:**

**Appearance:** white powder with faint yellow cast

**Structure:** This is a condensation product of p-methoxyphenethyl methylamine with formaldehyde; it is a mixture of low-molecular-weight polymers,  $6 \geq m \geq 3$ .<sup>1</sup> One claim is that the trimer is most active<sup>1</sup>, but another source cites the hexamer as being of highest activity. The monomer unit is  $C_{11}H_{13}NO$  (FW 153).<sup>3</sup>



**STORAGE / STABILITY AS SUPPLIED:**

The material has a shelf-life of at least five years when stored dry and at or below 25°C.<sup>1</sup>

**SOLUBILITY / SOLUTION STABILITY:**

The compound is tested at 50 mg/mL in water, giving a clear solution (per specifications, ranging from colorless to yellow in appearance). Solutions can be autoclaved at 15 psi for 30 minutes with no detectable change in toxicity or potency.<sup>1</sup>

**GENERAL USAGE:**

Compound 48/80 was first described as a blood pressure lowering agent, then recognized as a potent histamine releasing agent (primarily from mast cells, with a subsequent depletion of tissue histamine lasting over 48 hours.<sup>1</sup> It is the action of mast cell mediators on the cardiovascular system that is affected, and leads to circulatory collapse.<sup>4</sup> It is a condensation product of p-methoxyphenethyl methylamine with formaldehyde, and is a mixture of low-molecular-weight polymers, of which the hexamer is most active.<sup>2,5</sup> One reference indicates that it is toxic, that its toxicity is related to some action other than histamine release.<sup>6</sup> Compound 48/80 is a potent inhibitor of phospholipase C.<sup>7</sup>

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#### REFERENCES:

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